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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
BERTOGLIO, VALARIE E	

ART UNIT	PAPER NUMBER
1632	10

DATE MAILED: 10/06/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/876,143	EILERTSEN ET AL.	
	Examiner	Art Unit	
	Valarie Bertoglio	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *14 July 2003* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-60* is/are pending in the application.

4a) Of the above claim(s) *1-24 and 35-60* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *25-34* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *28 February 2002* is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☒ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *10,11,12* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Election/Restrictions

Applicant's election without traverse of Group V, claims 25-34 in Paper No. 14 is acknowledged.

Information Disclosure Statement

The listing of references in the specification is not a proper information disclosure statement. 37 CFR 1.98(b) requires a list of all patents, publications, or other information submitted for consideration by the Office, and MPEP § 609 A(1) states, "the list may not be incorporated into the specification but must be submitted in a separate paper." Therefore, unless the references have been cited by the examiner on form PTO-892, they have not been considered.

Specification

The disclosure is objected to because of the following informalities: The specification contains references to Tables 2 and 3 (page 95, line 28). The specification contains descriptions of Tables 1 and 2 (page 47, lines 16-20). However, no tables have been identified in the disclosure.

Appropriate correction is required.

Drawings

The drawings are objected to for the reasons listed on the attached form PTO-948 and for the following reasons. Figure 1 is too dark and the various regions of the pie chart cannot be distinguished or matched with the corresponding legend. A proposed drawing correction or

corrected drawings are required in reply to the Office action to avoid abandonment of the application. The objection to the drawings will not be held in abeyance.

Claim Rejections - 35 USC § 112-1st paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 25-34 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The specification describes a method of identifying cell lines that are developmentally competent nuclear donors. Specifically, the specification describes identifying from embryos ESTs, or molecular markers, that correlate with developmental competence. To identify the ESTs, microarray analysis of cDNAs derived from individual in vivo generated embryos and of an individual embryo generated by nuclear transfer using cell lines known to yield developmentally competent embryos was performed with comparison of each population of cDNAs and with cDNAs from embryos generated by nuclear transfer using cell lines known to not be capable of giving rise to developmentally competent embryos (pages 91-96). The specification describes identifying 13 cDNAs associated with two *in vivo* derived embryos and one nuclear transfer embryo derived from a cell line known to yield developmentally competent embryos. These 13 ESTs were not observed in two embryos derived from nuclear transfer using

two cell lines known to not be developmentally competent and were also not observed in nuclear transfer embryos derived from a previously uncharacterized line that failed to give rise to developmentally competent embryos (page 96, lines 12-13). One cDNA was identified as being present in the three developmentally incompetent cell lines and absent from the in vivo embryos as well as the embryos derived by nuclear transfer from the known, developmentally competent cell lines (page 96, lines 13-14).

Claims 25-29 are directed to a method of identifying a developmentally competent cell line comprising separating one or more cells from a cell line, performing nuclear transfer using nuclei isolated from said cell(s), and comparing the expression pattern of the nuclear transfer embryo to a gene expression database wherein the comparison identifies the embryos resulting from nuclear transfer from a developmentally competent cell. Claim 30 is directed to a method of producing one or more embryos by nuclear transfer, culturing the nuclear transfer embryo to at least the two-cell stage, separating at least one cell from the embryo and determining the developmental competence of the embryonic cell population by comparing the expression pattern of the nuclear transfer embryo to a gene expression database wherein the comparison identifies the embryos resulting from nuclear transfer from a developmentally competent cell. Claims 31-34 are directed to methods of assessing the effect of changes in a nuclear transfer protocol by performing nuclear transfer according to two nuclear transfer protocols and determining the developmental competence of the each of the two embryonic cell populations by comparing the expression pattern of each nuclear transfer embryo to a gene expression database wherein the comparison identifies the embryos resulting from nuclear transfer from a

developmentally competent cell and assessing the effect of the change by comparing the developmental competence of each nuclear transfer embryo.

The specification fails to be enabling for the claimed inventions for two reasons. First, the specification fails to provide the materials necessary to carryout the claimed invention, namely, the genes comprised by the database that are characteristic and indicative of developmental competence. Second, the claims as broadly written encompass comparison of expression profiles that have not been appropriately matched for variables that will affect the profiles such as species, developmental stage, and culture conditions.

The specification fails to enable claims 25-34 because it does not teach what nucleic acid molecules are associated with developmental competence of an embryo. The claimed invention requires comparing the expression profile of nuclear transfer embryos to a database but specification does not teach the contents of the database.

The art at the time of filing taught that the efficiency of cloning by nuclear transfer using a developmentally competent nuclear donor cell line is less than 2% (Pennisi et al., 2000, Science, Vol. 288, pages 1722-1727; Polejaeva, 2000, Nature, Vol. 407, pages 86-90; Westhusin, 2001, Theriogenology, Vol. 55, pages 35-49). The low frequency of live births is thought to be a result of the failure of donor nuclei to undergo reprogramming (Wells, Trends in Biotechnology, In Press; Polejaeva, page 86, column 2, paragraph 2). The art also held that in vitro culture of embryos affects transcription of some genes that are necessary for embryonic development (Niemann and Wrenzycki, 2000, Theriogenology, Vol. 53, pages 21-34; Niemann, 2002, Cloning Stem Cells, Vol. 4, pages 29-38). Gene expression profiles also differ for nuclear transfer embryos derived from the same cell line depending on the nuclear transfer protocol used as well

as a number of other parameters (Wrenzycki, 2001, Biology of Reproduction, Vol. 65, pages 309-317; Daniels, 2001, Molecular Reproduction and Development, Vol. 60, pages 281-288).

The specification teaches a large degree of heterogeneity between the expression profiles of in vivo derived embryos and nuclear transfer embryos derived from both developmentally competent and developmentally incompetent from cell lines cell lines (page 91, lines 17-28 and page 95, lines 7-26). Using differential display, it was observed that the mRNA profiles for multiple individual nuclear transfer embryos differ from that of in vivo by 73% for those derived from a developmentally competent cell line and 74% for those derived from a developmentally incompetent cell line (page 91, lines 24-27). Thus, there is a significant and general difference between the expression profiles of nuclear transfer embryos and *in vivo* derived embryos. However, there is a much smaller difference in banding pattern between nuclear transfer embryos derived from developmentally competent and developmentally incompetent cells. Thus, it would be an arduous task to determine which of the 27% of genes shared by the *in vivo* and nuclear transfer embryos derived from developmentally competent cells are indicative of developmental competence and the specification does not teach that the difference between the groups of nuclear transfer embryos is reflective of genes that are necessary for development.

Using microarray analysis, the specification teaches identification of 13 ESTs associated with 2 in vivo derived embryos and 1 NT derived embryo that was derived from a known developmentally competent cell line. The specification teaches that these 13 gene sequences were not associated with nuclear transfer embryos derived from cell lines that do not give rise to any developmentally competent embryos (page 96, lines 6-13). The specification, however, did not teach that the single nuclear transfer embryo derived from a cell line known to be

developmentally competent was, itself, properly reprogrammed and competent to become a viable animal. As set forth by the art, gene expression profiles vary in nuclear transfer embryos derived from the same cell line. Therefore, the gene expression profile of this particular embryo may not reflect the developmental competence of the cell line in general. Given the level of success in the art of less than 2% of nuclear transfer embryos developing into a live animal (see above), it is not possible to determine with any degree of confidence, the developmental competence or likelihood of viability until birth of any particular embryo derived from a developmentally competent cell line and it is statistically unlikely that the one nuclear transfer embryo examined represents a properly reprogrammed developmentally competent embryo. Therefore, based on the limited information provided in the specification, it cannot be determined that the 13 ESTs that the single nuclear transfer embryo share with the in vivo derived embryo are indicators of developmental competence of the donor cell line because it is not known that the embryo was properly reprogrammed, was itself developmentally competent, and represented the gene expression profile necessary for an embryo to give rise to a viable animal.

Ultimately, the specification fails to teach what genes correlate with developmental competence; it merely states that they were expressed in a single embryo derived from a developmentally competent cell line wherein the cellular reprogramming and developmental competence of said embryo was uncharacterized. The specification teaches 88% similarity in expression profile of 744 cDNAs compared between *in vivo* derived and the single nuclear transfer embryo derived from a developmentally competent cell line. Without knowing whether the nuclear transfer embryo was properly reprogrammed, one does not know how to interpret this

result. Is the 12% difference indicative of genes necessary for developmental competence of the embryo because the embryo failed to undergo proper reprogramming? Or, if the embryo were properly reprogrammed and is developmentally competent, one would look for genes among the 88% that are necessary for development. The specification does not definitively correlate the 13 genes mentioned as being commonly expressed in *in vivo* and nuclear transfer embryos with developmental competence (page 96, lines 11-13). The specification also fails to list the 13 genes. In order to determine what these genes are and if they definitively correlate with developmental competence, one must characterize gene expression in an embryo known to be competent to develop into an animal, not just an embryo derived from a cell line known to be developmentally competent. The specification does not teach any means of making this assessment other than through the claimed invention itself. Therefore, it would require one of skill in the art at the time the invention was made, undue experimentation to determine what nucleic acids are preferentially expressed in developmentally competent embryos in order to use the claimed invention.

Additionally, the following issues must also be addressed. The breadth of the claims are such that they encompass comparing expression profiles of embryos of different species, of embryos in different stages of development, and of embryos derived and cultured through different means. It was known in the art at the time of filing that different species follow different developmental programs (for example, refer to Oback, 2002, Cloning and Stem Cells, Vol. 4, page 169, column 2). For example, cellular differentiation begins at different stages of development in various species. It was also known in the art that embryos derived through in vitro means, including in vitro fertilization and nuclear transfer, show altered temporal

development in comparison to in vivo derived embryos (Niemann and Wrenzycki, 2000; specification page 91, lines 22-24). Other variables that effect the developmental reprogramming and gene expression of a nuclear transfer embryo include time between nuclear transfer and oocyte activation, passage number of the donor cell line, culture conditions of the donor cell line and culture conditions of the nuclear transfer embryo (Wrenzycki, page 312, column 2; Daniels, pages 281-288; Dobrinsky et al., 1996, Biology of Reproduction, page 1072, paragraph bridging columns 1 and 2). Gene expression profiles will differ at any given developmental stage between species of animals and will differ between various stages of development for a given species of animal (refer to specification, page 93, lines 11-13). These differences in expression will obscure any differences in gene expression that may be related to developmental competence. Therefore, claims should be limited to comparing embryos of like species at comparable stages of development.

Therefore, in light of the breadth of the claims, the lack of direction provided in the specification as to what genes indicate developmental competence of an embryo and the parameters necessary to assess developmental competence of an embryo, and the state of the art establishing that the rate of successful reprogramming and development of nuclear transfer embryos is extremely low, it would require one of skill in the art undue experimentation to determine how to practice the claimed invention.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 25-34 are rejected under 35 U.S.C. 102(b) as being anticipated by De Sousa (1999, Cloning, Vol. 1, pages 63-69).

De Sousa taught harvesting fetal fibroblast cells for use in nuclear transfer (page 64, column 2, last full paragraph). The fetal fibroblast cells were used in nuclear transfer (page 65, column 1, lines 9-13). The nuclear transfer embryos were pooled and the mRNA profile of the pool was compared to that of fetal fibroblast cells, embryonic cell donor nuclear transfer embryos and *in vivo* derived blastocysts (Figure 1).

De Sousa anticipates the claims, as broadly written. Use of individual fetal fibroblast cells cultured in vitro as nuclear donors constitutes separating one or more cells from a cell line and performing one or more nuclear transfer procedures. Comparing the mRNA expression profile of the resulting nuclear transfer embryos to that of *in vivo* derived embryos constitutes comparison of a plurality of nucleic acid molecules obtained from each of said embryos to a gene expression database. While De Sousa and the instant invention differ in that used pools of nuclear transfer embryos for expression analysis and the specification teaches using individual embryos, the claims as broadly written, encompass the analysis of pooled embryos. Accordingly De Sousa anticipates the claimed invention.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Valarie Bertoglio whose telephone number is 703-305-5469. The examiner can normally be reached on Mon-Weds 6:00-2:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Deborah Reynolds can be reached on 703-305-4051. The fax phone number for the organization where this application or proceeding is assigned is (703) 872-9306.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-1234.

Valarie Bertoglio
Examiner
Art Unit 1632

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